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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,814	SLIJKHUIS ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *19-24,30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,25-29,31 and 33-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 07/474,798.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-46 are pending in the application.

[2] Receipt of a substitute specification, filed April 19, 2004, is acknowledged.

[3] Applicants' amendment to the abstract, filed April 19, 2004, is acknowledged.

Restriction/Election

[4] Applicant's election with traverse of the invention of Group I, claims 1-18, 25-29, 31, and 33-36, filed April 19, 2004, is acknowledged. The elected invention is drawn to an expression cassette, a recombinant host cell, and a process for the preparation of an exogenous protein(s).

[5] Response to traverse: Applicants traverse the restriction requirement by arguing: 1) the restriction requirement incorrectly characterizes the two inventions as being related as product and process of use as both groups have process claims; 2) the rationale for demonstrating distinctness of the inventions addresses only a small part of the scope of the invention of Group I and fails to make the case that the host cell and process claims of Group I are distinct from the invention of Group II. Applicants' argument is not found persuasive.

Addressing argument 1), while it is acknowledged that both Groups I and II have process claims, Group II nonetheless is a method of using the nucleic acid of Group II. Under current Office practice, methods of making a polypeptide using a polynucleotide are typically included with claims drawn to the

polynucleotide. Thus, the examiner has included claims drawn to methods of using the claimed polynucleotide for producing a polypeptide with polynucleotide claims. However, the claims of Group II are not drawn to methods of producing a polypeptide and are instead drawn to processes of selective biochemical oxidation. In accordance with MPEP 806.05(h), these claims are related as being a product and a process of using that product, and consequently the inventions are distinct as the nucleic acid of Group I can be used for another process, such as a probe in a hybridization reaction. MPEP 806.05(h) states, "[i]f the applicant either proves or provides a convincing argument that the alternative use suggested by the examiner cannot be accomplished, the burden is on the examiner to support a viable alternative use or withdraw the requirement." In this case, it is undisputed that the invention of Group II is a method of using the invention of Group I and applicants have failed to prove or provide a convincing argument that the alternative use suggested by the examiner cannot be accomplished. Thus, the examiner properly restricted the claims.

Addressing argument 2), it is noted that even the claims drawn to host cells and methods of making a protein encompassed by Group I are independent or distinct from the method of Group II as the host cell can be used for another method, such as recombinant protein production, and the method of producing a protein encompasses different steps and yields different results from the method of Group II. Thus, ALL claimed subject matter encompassed by the invention of Group I is independent or distinct from the invention of Group II.

[6] The requirement is still deemed proper and is therefore made FINAL.

[7] Claims 19-24, 30, and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[8] Claims 1-18, 25-29, 31, and 33-46 are being examined on the merits.

Drawings

[9] The drawings are objected to because the "Brief Description of the Figures" section of the substitute specification filed April 19, 2004 does not correspond to the drawings filed February 26, 2002. Appropriate correction is required.

Specification/Informalities

[10] The specification is objected to as it does not conform to the following requirement(s): 37 CFR 1.52(b)(2)(iii), which requires only a single column of text and 37 CFR 1.52(b)(3), which requires that the claims must commence on a separate sheet. Appropriate correction is required.

[11] The abstract is objected to as it does not conform to the requirement(s) set forth in 37 CFR 1.52(b)(4), which requires the abstract to commence on a separate sheet. Appropriate correction is required.

[12] Reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78) is acknowledged. However, this reference to prior applications appears to be in error as, according to the reference, the instant application is a continuation of 07/474,857 AND 08/002,608. Further, it is noted

that application 07/474,798 appears to have been identified as "09/474,798." It is suggested that applicants correctly state the reference to prior applications in the first paragraph of the specification.

[13] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: Expression Cassettes Encoding Enzymes Catalyzing the Oxidation of Cholesterol to Pregnenolone.

Claim Objections

[14] Claim 2 is objected to in the recitation of "which are functional of catalyzing." It is suggested that the term be replaced with, for example, "which are capable of catalyzing" or "which function to catalyze."

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[15] Claims 1-3, 5-7, 13-18, 25-29, 31, 39-41, and 45-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 1 (claims 2-3, 5-7, and 13-18 dependent therefrom) is confusing in that "the corresponding control sequences effective in said host" is listed as

being a species of a genus of oxidation steps in hydrocortisone biosynthesis (see claim 1, bottom). It is suggested that applicants clarify the meaning of the claim.

[b] Claim 7 is unclear in the recitation of "a protein from the group of Claim 3" as claim 3 fails to recite a "group" of proteins. It is suggested that applicants clarify the meaning of the claim.

[c] Claim 25 (claims 26-29 dependent therefrom) is indefinite in the recitation of "group comprising proteins which are functional… …of catalyzing an oxidation step in the biological pathway for conversion of cholesterol into hydrocortisone." As the phrase includes an open transitional phrase, i.e., comprising, it is unclear as to the scope of heterologous DNAs encompassed by the claim.

[d] Claim 31 recites the limitation "3[beta]-HSDH"." There is insufficient antecedent basis for this limitation in the claim. It is appears that the enzyme should be identified as "3[beta]-HSD" as used in claim 4 and has been interpreted as such.

[e] Claim 39 (claims 40-41 dependent therefrom) recites the limitation "[t]he recombinant host cell." There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to recite, for example, "[a] recombinant host cell."

[f] Claims 45-46 are confusing as depending from claim 47 as there are only 46 claims in the instant application. It is suggested that applicants correct the dependency of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[16] Claims 1-8, 13-18, 25-29, 31, and 33-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

The claims are drawn to (in relevant part) a genus of expression cassettes comprising heterologous DNA encoding various enzymes, a genus of host cells including progeny thereof comprising said genus of expression cassettes, and methods of the production of a genus of exogenous proteins using said genus of host cells.

The claims are rejected because the specification fails to provide a sufficient description of the claimed genus of expression cassettes as the specification merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from

others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of expression cassettes, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the heterologous DNA(s) of the expression cassettes from other heterologous DNA(s) such that one can visualize or recognize the identity of the members of the genus. Furthermore, for claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses the following representative species of expression

vectors: pGBSCC-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, and –17; pGB17alpha-1, -2, -3, -4, and –5; pGBC21-1, -2, -3, -4, -5, -6, -7, -8, and –9; and pGB11beta-1, -2, -3, and –4. The specification fails to disclose even a single representative species of host cell progeny. The species encompassed by the genera of expression cassettes, host cells, including progeny thereof, and produced polypeptides encompasses widely variant species. Given the lack of description of a representative number of host cell progeny, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[17] Claims 1-8, 13-18, 25-29, 31, and 33-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the expression vectors of: pGBSCC-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, and –17; pGB17alpha-1, -2, -3, -4, and –5; pGBC21-1, -2, -3, -4, -5, -6, -7, -8, and –9; and pGB11beta-1, -2, -3, and -4, host cells transformed with said expression vectors, and a method of producing proteins by culturing said host cells, does not reasonably provide enablement for the broad scope of claimed expression cassettes, host cells, including progeny thereof, and methods of for making proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to

be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass: expression cassettes comprising a vast number of heterologous DNAs having various enzymatic activities (as encompassed by the claims) from any source, including mutants and variants of naturally occurring encoding heterologous DNAs; any protein encoded by the expression cassette; and any host cell progeny, having any variation in the characteristics of the parental host cell. The broad scope of claimed expression cassettes, host cells, including progeny thereof, and methods of making polypeptides is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of heterologous DNAs, polypeptides produced therefrom, and host cell progeny as broadly encompassed by the claims. In this case the disclosure is limited to the expression vectors of pGBSCC-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, and –17; pGB17alpha-1, -2, -3, -4, and –5; pGBC21-1, -2, -3, -4, -5, -6, -7, -8, and –9; and pGB11beta-1, -2, -3, and -4, host cells

transformed with said expression vectors, and a method of producing proteins by culturing said host cells.

- The lack of working examples and direction in the specification: The specification provides the following working examples: isolation of the heterologous DNAs within the expression vectors of pGBSCC-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, and –17, construction of these expression vectors, and methods for producing polypeptides therefrom. The specification fails to provide direction regarding the isolation of other heterologous DNAs that encode enzymes having the desired characteristics (as encompassed by the claims) from other organisms – if at all present. Further, the specification fails to provide guidance for altering the sequence(s) of the parent nucleic acid(s) with an expectation of obtaining an encoding nucleic acid with the desired characteristics.

- The high level of unpredictability in the art: In view of the lack of guidance in the specification, a skilled artisan would recognize the high level of unpredictability in isolating and making the broad scope of claimed expression cassettes. There is no indication in the specification as to which organisms are likely to have the desired nucleic acid or those nucleotides of the nucleic acid that are likely to be useful for identifying a corresponding nucleic acid in another organism, e.g., a nucleic acid region that is highly conserved among all members. Furthermore, one of skill recognizes the high level of unpredictability in altering an encoding nucleic acid with an expectation of obtaining the desired

enzyme. The nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Also, regarding claims drawn to host cell progeny, it is noted that it is highly unpredictable as those characteristics of the host that may be altered during culturing of any host cell.

- The state of the prior art supports the high level of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects

caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability… …they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no method for reasonably predicting the effects of even a *single* amino acid mutation on a protein, as evidenced by Witkowski et al. (*Biochemistry* 38:11643-11650), who teach that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

- The amount of experimentation required is undue: While methods of isolating homologues/orthologues of an encoding nucleic acid are known, e.g., by hybridization, and methods of generating variants of a given polypeptide by altering the encoding nucleic acid sequence are known, e.g., by site-directed mutagenesis, it is not routine in the art to screen for all heterologus DNAs from any source and/or having a substantial number of substitutions or modifications as encompassed by the instant claims.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the significant amount of experimentation required, undue experimentation would clearly be necessary for a skilled artisan to make the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

[18] Claims 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel vectors. Since the vectors are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed vectors' sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and

freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the plasmids. The specification does not disclose a repeatable process to obtain the vectors and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of these vectors should have been made in accordance with 37 CFR 1.801-1.809.

If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the vectors have been deposited under the Budapest Treaty and that the vectors will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

4. the deposit will be replaced if it should ever become inviable.

Claim Rejections – Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[19] Claims 2-3, 6-7, 25-26, 28-29, 33-37, and 39-44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 13-16, and 21 of US Patent 5,869,283 ('283 Patent). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 2-3, 6-7, 25-26, 28-29, 33-37, and 39-44 of the instant application are generic that all that is recited in claims 1-7, 13-16, and 21 of the '283 Patent, i.e., claims 2-3, 6-7, 25-26, 28-29, 33-37, and 39-44 are anticipated by claims 1-7, 13-16, and 21 of the '283 Patent.

[20] Claims 2-3, 6-7, 25-26, 28-29, 33-37, and 39-44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of US Patent 6,171,836 ('836 Patent). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 2-3, 6-7, 25-26, 28-29, 33-37, and 39-44 of the instant application are generic that all that is recited in claims 1-11 of the '836 Patent, i.e., claims 2-3, 6-7, 25-26, 28-29, 33-37, and 39-44 are anticipated by claims 1-11 of the '836 Patent.

[21] Claims 2-3, 6-7, 25-26, 28-29, 34-37, and 39-44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as

being unpatentable over claims 34-43 of copending Application No. 10/462,128. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 2-3, 6-7, 25-26, 28-29, 34-37, and 39-44 of the instant application are anticipated by claims 1-11 of copending Application No. 10/462,128.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

> A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).
>
> A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

[22] Claims 2-18, 25-29, 31, and 33 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 2-18, 25-29, 31, and 33 of copending Application No. 10/462,128. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[23] Applicant's claim to domestic priority under 35 USC §§ 120 and 121 to US non-provisional applications 09/098,990, 08/418,085, 08/054,185, 08/002,608, 07/474,857, and 07/474,798 is acknowledged. Applicants' claim to foreign priority under 35 USC § 119(a-d) to foreign-filed applications Netherlands 88202080.3, filed 09/23/88, Netherlands 88200904.6, filed 05/06/88, and PCT/NL89/0072 is acknowledged. It is noted that the earliest filed US non-provisional applications, 07/474,857, and 07/474,798 were filed more than one year after the filing of Netherlands 88202080.3 and Netherlands 88200904.6. Therefore, foreign priority has been granted only to the filing date of PCT/NL89/0072.

[24] Claims 1, 4-5, 13, 16-18, and 25-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Zuber et al. (Proc Natl Acad Sci USA 85:699-703). The claims are drawn to an expression cassette comprising heterologous DNA encoding an enzyme catalyzing an oxidation step in the conversion of cholesterol to hydrocortisone. Zuber et al. teach co-transfection of COS-1 (monkey kidney) cells with individual expression vectors each encoding bovine P450 side-chain cleaving enzyme (P450scc), steroid hydroxylase 17alpha-hydroxylase cytochrome P450 (P450-17alpha), and adrenodoxin (ADX), resulting in the expression of the encoded polypeptides. This anticipates claims 1, 4-5, 13, 16-18, and 25-26 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[25] Claim(s) 2-3, 6-8, 14, 34, 36-39, and 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zuber et al. (supra) in view of Sedlaczek et al. (Crit Rev Biotechnol 7:187-236) and Bulow et al. (Ann NY Acad Sci 501:44-49). The claims are drawn to expression cassettes comprising heterologous DNA encoding at least two enzymes in the biochemical conversion of cholesterol to hydrocortisone, host cells comprising said expression cassettes, and processes for producing proteins using said host cells.

Zuber et al. disclose the teachings as described above. Additionally, Zuber et al. teach that co-expression of P450ssc and ADX in COS-1 cells results in the increased production of pregnenolone (page 699, left column). Zuber et al. do not teach co-expression of P450ssc and ADX from a single expression vector.

Sedlaczek et al. review the state of the art regarding biotransformation of steroids, teaching particularly that pregnenolone is a commercially valuable steroid (pp. 187-188) and the use recombinant DNA technology to construct "tissue culture lines that may produce sterols… …in good yield" (pp. 216-217).

At the time of the invention, the use of fusion enzymes to link metabolic enzymes was a well known practice. Bulow et al. teach that such fusion enzymes have advantages over individually expressing the component enzymes such as, inter alia, stoichiometric production and proximity effects (pp. 44 and 49).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Zuber et al., Sedlaczek et al., and Bulow et al. to fuse and insert the genes encoding P450ssc and ADX into a single expression vector, transform COS-1 cells and use the cells for the production of pregnenolone. One would have been motivated to make such an expression vector and host cell in order to produce pregnenolone because of the teachings of Sedlaczek et al. as described above. One would have a reasonable expectation of success for fusing and inserting the genes encoding P450ssc and ADX into a single expression vector, transforming COS-1 cells and using the cells for the production of pregnenolone because of the results of Zuber et al., Sedlaczek et al., and Bulow et al. Therefore, claims 2-3, 6-8, 14, 34, 36-39, and 42-45, drawn to expression vectors, host cells, and methods for making proteins as described above, would have been obvious to one of ordinary skill in the art.

[26] It should be noted that claims 15, 28-29, 40-41, and 46 limit the claimed recombinant host cell to a microorganism and optionally to a particular genus of microorganism. These claims have not been rejected as being obvious because evidence provided at the time of the invention by Yabusaki et al. (US Patent 5,137,822) indicates that a skilled artisan would not have been motivated to express bovine P450ssc in Saccharomyces cerevisiae, a commonly utilized yeast for recombinant mammalian protein expression. Yabusaki et al. disclose the following regarding their efforts to express P450ssc in S. cerevisiae:

> The present inventors have also constructed expression plasmids by inserting the DNA sequence coding for adrenal cytochrome P-450scc, which has a side-chain cleaving activity against cholesterol, in an

> expression plasmid containing the ADH promoter and transformed Saccharomyces cerevisiae with the resulting plasmids, but the transformant yeasts only produced inactive P-450scc with no heme in its molecule. Thus, it was found that it was very difficult to forecast whether or not a particular mammalian P-450 species was able to successfully be expressed in given circumstances, and that each mammalian P-450 species differed from others in terms of its expressible conditions.

In view of this disclosure, one would not have been motivated to use a microorganism – particularly yeast – for the expression of bovine P450ssc as Yabusaki et al. teach away from transforming yeast with an expression vector encoding P450ssc.

[27] Claim(s) 1, 4, 13-15, 17, 25, 28-29, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over The et al. (Mol Endocrinol 3:1310-1312) in view of Sedlaczek et al. (Crit Rev Biotechnol 7:187-236). The claims are drawn to expression cassettes comprising heterologous DNA encoding an enzyme in the biochemical conversion of cholesterol to hydrocortisone and optionally wherein the enzyme is 3beta-HSD, host cells comprising said expression cassettes, and processes for producing proteins using said host cells.

The et al. teaches the cDNA encoding human 3beta-HSD and a method of isolation thereof (see particularly page 1311). The et al. teach 3beta-HSD is a key enzyme in the biosynthesis of all classes of hormonal steroids. The et al. teach the importance of 3beta-HSD and express a desire to "obtain more information about this crucial enzyme" (page 1310, bottom). The et al. does not teach an expression vector comprising their cDNA.

At the time of the invention, recombinant expression of a desired protein using a bacterial host, primarily E. coli, was well-known in the art. For example,

Sedlaczek et al. teach the use of recombinant DNA technology to for bacterial protein expression by incorporating an enzyme-encoding nucleic into a plasmid for expression in bacteria (page 216, bottom).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of The et al. and Sedlaczek et al. to incorporate the nucleic acid of The et al. into an expression vector, transform E. coli with said expression vector, and express the encoded protein using said transformed E. coli. One would have been motivated to express the encoded protein using said transformed E. coli in order to obtain sufficient quantities of 3beta-HSD in order to obtain more information about the enzyme as suggested by The et al. One would have a reasonable expectation of success for expressing the encoded protein using said transformed E. coli because of the results/teachings of The et al. and Sedlaczek et al. Therefore, claims 1, 4, 13-15, 17, 25, 28-29, and 31, drawn to expression cassettes, host cells, and methods for making proteins as described above, would have been obvious to one of ordinary skill in the art.

Conclusion

[28] Status of the claims:

- Claims 1-46 are pending.
- Claims 19-24, 30, and 32 are withdrawn from consideration.
- Claims 1-18, 25-29, 31, and 33-46 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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